VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1-3, 9, 11, 14, 15 and 20 have been amended as follows.

1. (Amended) A polynucleotide comprising a first promoter [derived] from a gene encoding a CD80 (B7-1) or a CD86 (B7-2) co-stimulatory molecule and a first sequence encoding at least one antigen wherein said first sequence is operably linked to said first promoter.

2. (Amended) The polynucleotide of claim 1, wherein the promoter is [derived] from a CD80 (B7-1) gene.

3. (Amended) The polynucleotide of claim 1, wherein the promoter is [derived] from a CD86 (B7-2) gene.

9. (Amended) A core carrier coated with [a] the polynucleotide according to claim 1.

11. (Amended) A pharmaceutical composition, comprising [a] the polynucleotide according to claim 1 and a pharmaceutically acceptable excipient.

14. (Amended) A method for eliciting an immune response in a vertebrate subject, said method comprising:

(a) providing a nucleotide sequence encoding an antigen operably linked to a promoter [derived] from a gene encoding a CD80 (B7-1) or a CD86 (B7-2) co-stimulatory molecule, said promoter capable of directing the expression of said antigen in the subject; and

(b) administering the nucleotide sequence to the subject, whereby the antigen is expressed in an amount sufficient to elicit an immune response.

15. (Amended) The method of claim 14, wherein the co-simulatory molecule is CD80 [or CD86].

20. (Amended) A method for eliciting an immune response in a vertebrate subject, said method comprising:

(a) providing a core carrier particle coated with a nucleotide sequence encoding at least one antigen, said nucleotide sequence operably linked to a promoter [derived] from a gene encoding a CD80 (B7-1) or a CD86 (B7-2) co-stimulatory factor, wherein said promoter is capable of driving expression of the antigen-encoding sequence in the subject; and

(b) administering the coated particle to the subject using a particle-mediated transdermal delivery technique, whereby the antigen is expressed in an amount sufficient to elicit an immune response.

In the Figures:

Please replace Figures 1-7 with new Figures 1-7 attached hereto.

REMARKS

Introductory Comments:

Claims 1-41 are pending in the application. Applicants note with appreciation that the Office has acknowledged applicants' election of Group I, claims 1-25, as provided for in the Response filed 19 March 2002. Claims 26-41 have been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as drawn to a non-elected invention.

Accordingly, claims 1-25 are currently under consideration and were examined in the Office Action dated 24 April 2002. In the Action, the Office has asserted the following objections and claim rejections: (1) the specification was objected to as informal; (2) claims 1-25 stand rejected under 35 U.S.C. § 112, first paragraph, as inonenabled; (3) claims 1-3, 9, 11, 14 and 20 stand rejected under 35 U.S.C.§112, second paragraph, as indefinite; (4) claims 1-3, 11 and 14-15 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 6,339,068 to Krieg et al. ("Krieg") when taken with Ellis et al. (1996) *J. Immunol.* 56:2700-2709 ("Ellis") and further in view of either Zhang et al. (1996) *Gene* 183:1-6 ("Zhang") or Li et al. (2000) *Human Immunology* 61:486-698 ("Li"); (5) claims 1-5 and 11-19 stand rejected under 35 U.S.C. §103(a) as unpatentable over Krieg, Ellis and either Zhang or Li when taken with any of Gurunathan et al. (1998) *J. Immunol.* 161::4563-4571 ("Gurunathan"), Pulendran et al. (1998) *J. Exp. Med.* 188:2075-2082 ("Pulendran") or Wong et al. (1997) *J. Exp. Med.* 186:2075-2080 ("Wong"); and (6) claims 1-5 and 9-25 stand rejected under 35 U.S.C. §103(a) as unpatentable over Krieg, Ellis, and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong in further view of Lai et al. (1995) *DNA and Cell Biol.* 14:643-651 ("Lai").

All standing objections and claim rejections are respectfully traversed for the reasons discussed herein below.

Overview of the Amendments:

Applicants, by way of this Amendment, have provided minor amendments to claims 1-3, 9, 11, 14, 15 and 20, and have entered minor amendments to Figures 1-7. More particularly, claims 1-3, 14 and 20 have been amended to remove the term "derived" that was objected to by the Office. Claims 1, 14 and 20 have also been amended to now recited CD80 or CD86 co-stimulatory molecules. Finally, claims 9 and 11 have been amended merely to change "a" to "the" at the request of the Office. Support for these claim amendments can be found throughout the specification and claims as originally filed. Accordingly, no new matter has been added by way of these claim amendments, and the entry thereof is respectfully requested.

Applicants have also provided re-drawn figures 1-7 where the reference characters, numbers, lines and letters have merely been darkened and clarified where appropriate. Applicants submit that no new matter has been added by way of the re-drawn figures, and the entry thereof is respectfully requested.

The Objection to the Specification:

The specification was objected to as informal on the basis that a line appears at line 21 of page 63 in the specification. Clarification was requested.

In response, applicants note that the subject line was provided merely to represent the demarcation between the specification and the claims. Reconsideration and withdrawal of the objection is thus respectfully requested.

The Rejections under 35 U.S.C. §112, first paragraph:

Claims 1-25 stand rejected under 35 U.S.C. §112, first paragraph, on the basis of written description. In particular, the Office has objected to the term "derived", that is, that "the specification contemplates production of a genus of promoter derived from a gene encoding a co-stimulatory molecule." Office Action at page 3. The Office goes on to acknowledge that "the as-filed specification provides sufficient description of a promoter from a co-stimulatory molecule selected from either a CD80 or a CD86 gene." Office Action at page 3.

In response, applicants direct the Office's attention to the amendments to claims 1-3, 14 and 20, wherein the term "derived" has been deleted from the base claims, and claims 1, 14 and 20 have further been amended to recite promoters selected from either CD80 or CD86 molecules. Claims 4-13, 15-19 and 21-25 all depend either directly or indirectly from claims 1, 14 or 20, and thus now contain these same limitations. Accordingly, applicants submit that the rejection of claims 1-25 under 35 U.S.C. §112, first paragraph, has been overcome by way of the amendments submitted herewith. Reconsideration and withdrawal is thus respectfully requested.

Claims 1-25 further stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled. In particular, the Office notes that the specification is enabling for CD80 or CD86 promoters, but not for promoter "derived" from other co-stimulatory molecules. Office Action at pages 5-9.

In response, applicants again direct the Office's attention to the amendments to claims 1-3, 14 and 20, wherein the term "derived" has been deleted from the base claims, and claims 1, 14 and 20 have further been amended to recite promoters selected from either CD80 or CD86 molecules. Claims 4-13, 15-19 and 21-25 all depend either directly or indirectly from claims 1, 14 or 20, and thus now contain these same limitations.

Accordingly, applicants submit that the rejection of claims 1-25 under 35 U.S.C. §112, first paragraph, has been overcome by way of the amendments submitted herewith. Reconsideration and withdrawal is thus respectfully requested.

The Rejection under 35 U.S.C. §112, second paragraph:

Claims 1-3, 9, 11, 14 and 20 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, the Office first objects to claims 9 and 11 on the basis that they recite "a" polynucleotide of an earlier claim instead of "the" polynucleotide of an earlier claim.

In response, applicants direct the Office's attention to the amendments to claims 9 and 11 whereby applicants have changed "a polynucletode" to now read "the polynucleotide" as helpfully suggested by the Office. Accordingly, applicants submit that the rejection of claims 9 and 11 under 35 U.S.C. §112, second paragraph, has been overcome by way of the amendments submitted herewith. Reconsideration and withdrawal is thus respectfully requested.

The Office further objected to claims 1-3, 14 and 20 on the basis that these claims contain the "relative term derived". Office Action at pages 9 and 10. In response, applicants direct the Office's attention to the amendments to claims 1-3, 14 and 20 whereby applicants have deleted the term "derived" from the claims Accordingly, applicants submit that the rejection of claims 1-3, 14 and 20 under 35 U.S.C. §112, second paragraph, has been overcome by way of the amendments submitted herewith. Reconsideration and withdrawal is thus respectfully requested.

The Rejections under 35 U.S.C. §103(a):

Claims 1-3, 11 and 14-15 stand rejected under 35 U.S.C. §103(a) as unpatentable over the combination Krieg taken with Ellis and in further view of either Zhang or Li. More particularly, the Office asserts that Krieg teaches an immunostimulatory nucleic acid comprising at least one CpG-S motif and a nucleic acid encoding an antigen" and "using a cell specific promoter that is operative in antigen-presenting cells." Office Action at pages 10 and 11. However, the Office acknowledges that "Krieg did not teach explicitly that antigen presenting cell specific promoter is a co-stimulatory promoter obtained from a CD80 or CD86 gene." Office Action at page 11. The Office then asserts "however, at the time the invention was made, Ellis teaches that CD80 and CD86 genes are expressed only in antigen presenting cells ... Li teaches [the] 5'-regulatory region (promoter region) of human CD86 gene ... [and] Zhang teaches that the CD80 promoter is expressed only in APCs" Office Action at page 11. The Office then concludes "it would have been *prima facie* obvious ... to employ either the CD80 or CD86 promoter as the APC promoter in the method of Krieg" and "one would have been motivated to use CD80 or CD86 promoter.. In the construct of Krieg ... because the CD80 and CD86 genes were known to one of ordinary skill in the art to express in antigen presenting cells." Office Action at page 11. Applicants respectfully disagree.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the

benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submit that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over its asserted combination.

What the Office has done is to have identified discrete elements of applicants' recited combination (that is, to find nucleic acid vaccines in the primary reference by Krieg and then find CD80 or CD86 promoters in various of the secondary references) and then magically combine these elements--without finding the teaching or suggestion to have done so in the prior art! The Office submits that the motivation to make this untaught, undisclosed combination was simply that CD80 and CD86 promoters were known to the skilled artisan. This is clearly insufficient to establish a *prima facie* since it is the references (i.e., the prior art) that must suggest the desirability of making the combination, and not applicants' specification.

If knowledge of CD80 or CD86 promoters was really a suitable motivation as the Office would argue, why then did Krieg not teach or suggest that CD80 or CD86 promoters could or should be used in their constructs? Ellis and Zhang were published in 1996. Krieg was first filed in 1997 and then in 1998, clearly in light of the Ellis and Zhang publications for several eyars. Li was published in 2000, 3-4 years after Ellis, Zhang and Krieg and again clearly in light of Ellis and Zhang. Why did Li neglect to teach or suggest such an "obvious" combination? Why did not a single one of the references cited by the Office in the present Office Action teach or suggest such a combination in light of the Office's asserted motivation to have done so? If the Office is correct in its assertion that there was a proper motivation to produce applicants' recited combination merely on the basis that the promoters were known, and a field of skilled artisans somehow neglected to

make this simple combination over the course of 3-4 years, then what the Office has actually identified is a long-felt need in the art that was not met until applicants taught this combination. The presence of a long-felt need combined with the Office's asserted motivation is a clear indication of non-obviousness. *Graham v. John Deere Co.* 148 USPQ 459 (S. Ct. 1966).

Accordingly, the instant rejection is improper since the Office has failed to establish *prima facie* obviousness. Not only has the Office failed to identify the requisite teaching or suggestion to make applicants' recited combination, it has also established that there was a clear long-felt need to make applicants' combination that was not met until applicants filed their specification. For these reasons, then, the rejection of claims 1-3, 11 and 14-15 is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 1-5 and 11-19 stand rejected under 35 U.S.C. §103(a) as unpatentable over Krieg, Ellis, Zhang or Li taken with any of Gurunathan, Pulendran or Wong. More particularly, the Office asserts the rejection of the base claims 1 and 14 as applied above, however the Office acknowledges that "Krieg taken with Ellis in further view of either Li or Zhang do not teach explicitly that the APC specific promoter is obtained from a co-stimulatory promoter from CD80 or CD86 for use in [the method of] Krieg in combination with at least one cytokine selected from the group consisting of CD40L, TRANCE or Plt-3L {or a nucleotide sequence encoding such a cytokine]." Office Action at page 12. The Office seeks to fill in this missing teaching by arguing that Gurunathan describes CD40 ligand, Pulendran shows administration of Flt-3 ligand and Wong reports on TRANCE." Office Action at pages 12-13. The Office then concludes "it would have been *prima facie* obvious ... to combine the work of Krieg, Ellis and either Li or Zhang taken with any of Gurunathan, Pulendran or Wong ... to elicit an immune response in a vertebrate subject." Office Action at page 13. The Office asserts that "one of ordinary skill in the art would

have been motivated to [make the 7-way combination asserted by the Office] to assist in regulating the development of immune effector cells." Office Action at page 14. Applicants respectfully disagree.

As established herein above, the Office's initial 4-way combination of Krieg, Ellis, Li and Zhang clearly fails to teach or suggest applicants' specific combination of CD80/CD86 promoters in an antigen-expressing construct. The Office has merely shown that there was a long-felt need for applicants' recited base combination that simply was not met until applicants taught the solution to the long-felt need by way of their specification. The Office now argues that 3 additional references that merely discuss still further recited elements (TRANCE, and Flt-3 and CD40 ligands) somehow fill in all of the missing pieces. However, the Office has not pointed to any teaching or suggestion from the prior art itself, that is, from Krieg, Ellis, Zhang, Li, Gurunathan, Wong or Pulendran, to make this "obvious" combination--despite the asserted motivation that one would want to regulate the development of immune effector cells. Accordingly, the Office has clearly failed to establish its' *prima facie* showing of obviousness. There is nothing from the recited art that teaches or suggests applicants' specific recited combination. The Office has merely found bits and pieces of applicants' combination in completely disparate references, and then concocted an unsupportable "motivation" to have made this combination. There is nothing in the cited references that teach or suggest applicants' specific combination, so there cannot have been a reasonable expectation of success for this combination.

For all of the foregoing reasons, then, the rejection of claims 1-5 and 11-19 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 1-5 and 9-25 stand rejected under 35 U.S.C. §103(a) as unpatentable over Krieg, Ellis and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong, and

further in view of Lai. In particular, the Office has applied the rejections of the base claims 1 and 14 as above, but then acknowledges that "Krieg taken with Ellis in further view of either Li or Zhang or Kreig and Ellis in further view of either Li or Zhang taken with any of Gurunathan, Wong or Pulendran do not teach using an immunogenic composition comprising a core particle." Office Action at page 14. However, the Office asserts "at the time the invention was made, Lai teaches that a technique called biolistic transformation ... is rapid and specific for genetic immunization." Office Action at page 14. The Office then concludes "it would have been *prima facie* obvious ... to coat the construct of the combined references Krieg, Ellis and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong onto heavy tungsten or gold for transdermal delivery" and "one of ordinary skill in the art would have been motivated to have employed the microparticle injection ... because a gene gun for genetic immunization saves time, money and labor as taught by Lai." Office Action at page 15. Applicants respectfully traverse.

As established herein above, the Office's initial 4-way combination of Krieg, Ellis, Li and Zhang clearly fails to teach or suggest applicants' specific combination of CD80/CD86 promoters in an antigen-expressing construct. The Office has merely shown that there was a long-felt need for applicants' recited base combination that simply was not met until applicants taught the solution to the long-felt need by way of their specification. Furthermore, as also established herein above, the Office's subsequent 7-way combination of Krieg, Ellis, Li and Zhang with Gurunathan, Pulendran and Wong also clearly fails to teach or suggest applicants' specific combination of CD80/CD86 promoters in an antigen-expressing construct combined with specific cytokines or nucleotide sequences encoding such cytokines. The addition of Lai to this unwieldy assembly of individual documents each discussing individual elements of applicants' recited combination simply fails to provide the missing teaching or suggestion. Accordingly, the Office has failed to establish its showing of

prima facie obviousness over the combination of Krieg, Ellis, Li and Zhang with Gurunathan, Pulendran and Wong and Lai.

For these reasons, then, the rejection of claims 1-5 and 9-25 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal of the rejection is thus respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims as now pending define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect is earnestly solicited. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that the Examiner contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

Date: 24 October 2002

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